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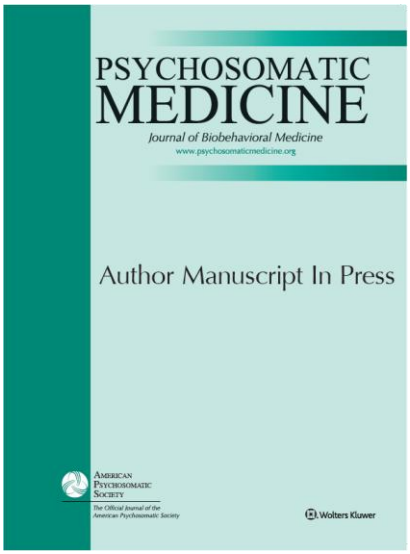


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# The association between selective serotonin reuptake inhibitors and glycemia: a systematic review and meta-analysis of randomized controlled trials

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**Abstract**

**Objective:**

Individual studies have reported conflicting effects of selective serotonin reuptake inhibitors (SSRIs) on glycaemia. We systematically reviewed the effects of SSRIs on glycemia and whether metabolic and psychological factors moderated these effects.

**Methods:**

We systematically searched for placebo-controlled randomised controlled trials (RCTs) investigating the effect of SSRIs on glycaemia (fasting blood glucose or HbA1c) as a primary or secondary outcome. Random-effects meta-analysis was conducted to compute an overall treatment effect. Meta-regression tested whether depression, type 2 diabetes, insulin resistance, treatment duration and weight loss moderated treatment effects.

**Results:**

Sixteen RCTs (*n*=835) were included and glycaemia was usually a secondary outcome. Overall, SSRIs improved glycaemia versus placebo (*pooled effect size (ES)*=-0.34, 95% confidence interval (CI) -0.48 to -0.21; $p < 0.001$, $I^2$=0%). Individually, fluoxetine (*ES*=-0.29, 95% CI -0.54 to -0.05; p=0.018) and escitalopram/citalopram (*ES*=-0.33, 95% CI -0.59 to -0.07; p=0.012) outperformed placebo, but paroxetine (*ES*=-0.19, 95% CI -0.58 to 0.19; p=0.33) did not. Results were similar in populations selected for depression as those not. Across studies, baseline insulin resistance (*p*=0.46), treatment duration (p=0.47), diabetes status (p=0.41) and weight loss (p=0.93) did not moderate changes. Heterogeneity for all analyses was non-significant.

**Conclusions:**

SSRIs appear to have an association with improvement in glycaemia, which is not moderated by depression status, diabetes status or change in weight across studies. Future powered trials with longer treatment duration are needed to confirm these findings.

**Registration:**

PROSPERO ID: CRD4201809239

**Keywords:**

Diabetes; depression; insulin resistance; systematic review, meta-analysis, meta-regression.

**Abbreviations:**

CI = confidence interval; ES = effect size; HOMA = Homeostatic Model Assessment; RCT = randomised controlled trial; SMD = standardised mean difference; SSRI = selective serotonin reuptake inhibitors.

## Introduction

Depressive symptoms are twice as common in people with type 2 diabetes compared to the general population and are associated with increased risk of diabetes complications and premature mortality (1, 2). The selective serotonin reuptake inhibitors (SSRIs) class of antidepressants are recommended as first-line pharmacotherapy for depression (3), as they are considered to have a favourable side effect profile. The effects of SSRIs are less well established in type 2 diabetes; while SSRIs consistently improve depressive outcomes (4), the evidence that they improve glycaemia and other biomedical outcomes is less consistent. A recent systematic review of observational studies reported that antidepressant use may in fact increase the risk of incident type 2 diabetes (5), although the causal basis of this association has been disputed (6). In randomised controlled trials (RCTs) of patients with type 2 diabetes and depression, some have reported benefits of SSRIs on both depression and glycaemia, whereas others have reported benefit for depression but not glycaemia (7).

A potential reason for the inconsistency in findings is the different types of SSRIs used. RCTs that have tested fluoxetine versus placebo have generally found improvements in glycaemia (8, 9), whereas other SSRIs such as paroxetine have not observed such positive effects (10). No previous meta-analysis has compared different types of SSRI for their effects on glycaemia. Another possible reason is different clinical groups: whilst some studies have tested SSRIs for glycaemia in patients with comorbid depression (7), others have not selected for depression (8, 9). Some studies have recruited non-diabetes patients with elevated insulin resistance (11), whilst others have recruited patients with established diabetes (12). Within the type 2 diabetes population, study samples have

varied from those who are insulin-requiring (13) to those still prescribed only oral diabetes medications (12).

With SSRIs proposed as both a potential cause and a potential therapy for diabetes, a clearer consensus regarding their effects on glycaemia is needed, as well as the metabolic and psychological moderators of such effects. We have therefore conducted a systematic review and meta-analysis of placebo-controlled RCTs, with the primary aim of testing whether SSRIs cause a change in glycaemia over time. Our secondary aims were to compare individual SSRIs for their respective effects on glycaemia, and to test for moderators of response, including comorbidity of depression, comorbidity of diabetes, elevated insulin resistance, treatment duration and weight loss.

## Methods

### Search strategy and selection criteria

The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14), in which studies that meet review criteria are examined and those that were RCTs and with sufficient data pooled for meta-analysis. The protocol was prospectively registered (PROSPERO ID CRD42018092397) (15).

We systematically searched the following databases from 1 January 1987 (as contemporary SSRIs were first used in this year) to 28 March 2018: EMBASE, PsycINFO, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. Additionally, unpublished trials were searched for in clinical trials databases such as ClinicalTrials.gov and the ISRCTN Register.

The following MeSH search strategy was implemented: "("Serotonin Uptake Inhibitors/blood"[Mesh] OR "Serotonin Uptake Inhibitors/therapeutic use"[Mesh]) AND ("Diabetes Mellitus, Type 2/drug therapy"[Mesh] OR "Diabetes Mellitus, Type 2/metabolism"[Mesh] OR "Diabetes Mellitus, Type 2/prevention and control"[Mesh] OR "Diabetes Mellitus, Type 2/psychology"[Mesh] OR "Diabetes Mellitus, Type 2/therapy"[Mesh])". Following this, a free text search was carried out in all databases using Boolean operators and truncation (*): "(ssri* OR "selective serotonin" OR fluoxetine OR citalopram OR escitalopram OR fluvoxamine OR sertraline OR paroxetine) AND (glycaemic OR glycemic OR glycaemia OR glycemia OR glucose OR diabetes OR diabetic OR "insulin resistance" OR "insulin sensitivity" OR "insulin secretion" OR "beta-cell function" OR homa-ir OR homa-b OR "metabolic factors") NOT (rat* OR mouse OR mice)". Where filters could be applied appropriately, the search was limited to clinical trials and human studies only.

Titles were reviewed and abstracts of all titles fulfilling the inclusion criteria were assessed. Full-text articles of abstracts meeting the inclusion criteria were examined and relevant studies were analysed for data extraction. The reference lists of included studies were checked for additional publications. Two authors (TT and CDM) independently performed the literature search and evaluated the studies for inclusion. Any disagreements were resolved through discussion with a third author (CWPH) and consensus reached.

The inclusion criteria were: (1) RCTs comparing any SSRIs with placebo, (2) glycaemia was measured, as a primary or a secondary outcome, using HbA1c or fasting blood glucose (FBG), (3) glycaemia was measured before and after the intervention and

placebo, (4) a minimum of 10 patients were recruited. The specific exclusion criteria were: (1) observational studies, (2) case reports or case series, (3) review articles or other secondary analyses not presenting original data, (4) pre-clinical studies performed *in vitro* or in animals, (5) RCTs involving active controls such as other antidepressants.

To maximise comparability of studies and to account most robustly for placebo effects on depression, only placebo-controlled RCTs were included. We included a range of studies examining patients with type 2 diabetes, patients without type 2 diabetes, as well as patients with and without depression, in order to elicit the impact of SSRIs on different subpopulations. However, because potential effects of SSRIs on insulin secretion were evaluated, we additionally excluded studies involving exclusively patients with type 1 diabetes or exclusively insulin-dependent type 2 diabetes, given that their endogenous insulin secretory function has a limited chance of recovery with pharmacotherapy (16).

**Data extraction and quality assessment**

The primary outcome was change in glycaemia, as measured by FBG or HbA1c. As FBG is more rapidly responsive to change (17), this was used as the primary data of extraction where presented. For each included study, the following additional data were extracted: sample size, mean age and sex of participants, baseline diabetes/metabolic status (including baseline insulin resistance and insulin secretion estimates), duration and dose of intervention and control, baseline BMI and change in weight, significant adverse effects, whether glycaemia was a primary or secondary outcome, and the mean change in FBG for intervention and control groups. If the raw value for mean change in FBG was not presented, this was estimated by subtracting baseline FBG from follow-up FBG. If the SD of the change score was missing, we used the square root of the average of the

baseline and follow-up variance in each group, thereby assuming that the correlation between the baseline and the follow-up outcome values was 0.5. If raw values for insulin resistance and secretion were not available, the Homeostatic Model Assessment (HOMA) formula (18), which uses FBG and fasting plasma insulin, was employed to derive these values. For studies including a subgroup of patients with insulin-dependent diabetes, the authors were contacted for data stratified by insulin use. If no response was received, the whole sample was included in order to extract the maximum available data.

The quality of studies was evaluated using the Cochrane Collaboration's tool for risk of bias (19). Whilst other quality assessment tools are numerical scales, empirical evidence suggests associations between such scales and treatment effect sizes are inconsistent and unpredictable (20). For each type of bias, two authors (TT and CWPH) independently judged the risk as low, high or unclear using the Cochrane Collaboration tool's criteria. Consensus discussion with a third author (CDM) was used to resolve differences.

**Statistical analysis**

Using the metan command in STATA 11.0, we performed meta-analysis for any individual SSRI tested in at least 3 RCTs. For each study, effect-size estimates were calculated using the standardised mean difference (SMD) in change in glycaemia following treatment. SMD is an appropriate measure of effect estimate when studies assess the same variable using different measures, such as FBG and HbA1c. SMD was calculated by dividing the mean difference by the pooled SD of each arm (equivalent to Cohen's d). Given that Cohen's d may produce a biased estimate of effect size in small studies where $n < 20$, this was converted into Hedges' $g$. The standard error (SE) of each study's group sizes was calculated according to a formula provided by Cooper and

Hedges (21). Next, studies were weighted using an inverse-variance method, studies with larger precision given greater weight. Pooled effect estimates were calculated using a random-effects model, which allows for heterogeneity between studies by permitting the true effects estimated by the studies to differ between studies. The combined effect thus represents the mean of the population of true effects and is appropriate where effects may vary between populations (22). This is expected in this meta-analysis where there is variation in medication, metabolic status, treatment duration and dose.

Forest plots were stratified firstly by type of SSRI, and citalopram and escitalopram were combined because of their similar molecular structure, as in previous meta-analyses (23). In order to define subgroups most likely to respond to treatment, the meta-analysis was repeated when stratified by presence/absence of depression and then presence/absence of diabetes at baseline. Heterogeneity between studies was quantified by calculating the $I^2$ statistic, which represents the fraction of variation between studies attributable to heterogeneity. Values for $I^2$ range between 0% and 100% with values of 25%, 50% and 75% suggesting low, moderate and high heterogeneity respectively (24).

Four independent sensitivity analyses were conducted: i) removing studies reporting HbA1c only; ii) removing studies involving any insulin-dependent patients; iii) removing studies reporting depression as a secondary outcome; and iv) removing small studies (recruiting less than 40 patients). Publication bias was assessed using a Funnel plot, Begg's Test and Egger's test (25). In order to define moderators of treatment response, we performed random-effects meta-regression using the following study-level covariates: baseline HOMA-IR (insulin resistance), baseline BMI, depression measured as a primary or secondary outcome (dummy coded 1 for primary, 0 for secondary),

diabetes status (dummy coded 1 for diabetes population, 0 for non-diabetes), treatment duration in weeks, and change in body weight. Baseline HOMA-B is directly proportional to HOMA-IR so was not also tested in meta-regression. Data on change in HOMA measures were only available for 3 studies and therefore were not used.

**Results**

A total of 2761 potentially relevant studies were identified. After reviewing titles, 105 abstracts were read and 42 full-texts further analysed. From these, 16 studies were included in meta-analysis (Figure 1), of which 8 (8, 9, 12, 26-30), 3 (10, 31, 32), 2 (11, 33), 1 (34), 1 (35) and 1 (36) studies tested fluoxetine, paroxetine, escitalopram, citalopram, sertraline and fluvoxamine respectively. Duration of studies ranged from 4 weeks to 12 months. Across all studies included in the meta-analysis, there were a total of 835 participants, with a mean age of 49.0 years and 47.1% of participants were male. Ten of the studies investigated patients with type 2 diabetes, of which 5 studies had comorbid depression. Only 4 studies measured glycaemia as a primary or co-primary outcome (10, 31, 34, 35). The majority of studies measured glycaemia using FBG and only 3 measured HbA1c (28, 32, 35) (Table 1). Risk of bias was low in most domains, excepting a high risk of attrition bias in 7 studies due to non-specification of intention-to-treat analysis, an unclear risk of selection bias in 10 studies due to lack of detailed explanation of allocation concealment procedures, and an unclear bias arising from pharmaceutical funding for 8 of the studies (Table 2). Aside from an increased incidence of tremor in one study, adverse effects were no more common in SSRI patients than placebo (26) (Table 3).

In the overall meta-analysis, SSRIs led to a significantly greater improvement in glycaemia compared to placebo (*pooled effect size (ES)* = -0.34, 95% CI -0.48 to -0.21; $p < 0.001$, $N_{studies} = 16$). The overall heterogeneity for the full meta-analysis was very low ($I^2 = 0\%$, $p = 0.63$). Of individual SSRIs, a beneficial effect of SSRIs was observed for fluoxetine (*ES* = -0.29, 95% CI -0.54 to -0.05; $p = 0.018$) and escitalopram/citalopram (*ES* = -0.33, 95% CI -0.59 to -0.07; $p = 0.012$). In contrast, paroxetine displayed a non-significant effect on glycaemia (*ES* = -0.19, 95% CI -0.58 to 0.19; $p = 0.33$). The heterogeneity for all subgroups was low and not significant. There were insufficient studies to perform a subgroup analysis on sertraline and fluvoxamine (Table 3, Figure 2).

In the subgroup of patient with diabetes at baseline, SSRIs significantly improved glycaemia compared to placebo (*ES* = -0.40 (95% CI -0.60, -0.21), $p < 0.001$, $N_{studies} = 10$). However, in non-diabetes populations, this effect was not significant (*ES* = -0.26 (95% CI -0.52, 0.01), $p = 0.061$, $N_{studies} = 6$) (Table 3, Figure 3). Similar effects of SSRI were seen in patients with depression (*ES* = -0.31 (95% CI -0.57, -0.06), $p = 0.015$, $N_{studies} = 5$) and those without depression (*ES* = -0.35 (-0.53, -0.18), $p < 0.001$, $N_{studies} = 11$) at baseline (Table 3, Figure 4). In random-effects meta-regression using study-level covariates, presence of diabetes (p= 0.41, $N_{studies} = 16$) baseline HOMA-IR ($p = 0.46$, $N_{studies} = 7$), baseline BMI ($p = 0.30$, $N_{studies} = 12$), duration of treatment (p=0.47, $N_{studies} = 16$), measuring depression as a primary or secondary outcome (p=0.87, $N_{studies} = 16$), and change in weight ($p = 0.93$, $N_{studies} = 12$) were not significantly associated with glycaemia treatment effect.

In sensitivity analyses, when respectively excluding studies reporting HbA1c; studies including any insulin-dependent patients; studies measuring depressive symptoms as a secondary outcome; or studies with less than 40 patients, the overall result did not significantly differ (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/PSYMED/A567). There was no evidence of publication bias: (Egger's test $p = 0.48$, symmetrical Funnel plot (Figure 5), Begg's test $p = 0.50$).

## Discussion

In this systematic review and meta-analysis of 16 RCTs, SSRIs had a positive overall effect on glycaemia compared to placebo. Of individual SSRIs, significant benefit was seen for fluoxetine and escitalopram/citalopram but not for paroxetine. The comorbidity of depression did not moderate the effects of SSRIs on glycaemia. SSRIs were generally well tolerated. Across studies, diabetes status, baseline insulin resistance, baseline BMI and change in weight were not associated with reduction in glycaemia in the treatment group, although between-study heterogeneity was very low.

### Comparison with previous literature

Two previous systematic reviews have tested the effects of SSRIs on glycaemia. Although well conducted, both were significantly limited by their scope, including only 5 studies each in their meta-analyses of SSRIs and glycaemia. The first included only fluoxetine studies (37), thereby excluding the majority of SSRIs, including those potentially more effective in treating depression (38). The second review was limited to patients with diagnosed depression and comorbid diagnosed diabetes (39), thereby excluding high-risk populations such as patients with obesity, who may also benefit from effects of SSRIs on glycaemia. By including 16 studies, our meta-analysis exhibits

increased power for testing the effects of SSRIs on glycaemia. Moreover, this is the first meta-analysis to compare the different SSRIs and include studies investigating patients without diabetes, or without depression, in order to assess generalisability.

Our findings contrast those of a systematic review of 22 observational studies of anti-depressants and diabetes, which concluded, of antidepressants, "caution is advised and a heightened alertness to the potential risk of diabetes is necessary" (40). However, the authors stressed that causality was not established and pointed out large inconsistencies across studies. Likewise, secondary analyses of the Diabetes Prevention Program have reported an association between antidepressant use and increased risk of incident type 2 diabetes (41). However, those receiving antidepressants at baseline had significantly higher CRP concentration (42), itself a robust risk factor for type 2 diabetes onset (43). This suggests that antidepressants are being given to people who are already at high risk of type 2 diabetes for other reasons. Whilst medical records studies have found evidence of weight gain following long-term use of some antidepressants (4), results of clinical trials have been conflicting and have consistently found weight-loss following fluoxetine treatment, at least in the short-term (45). Meanwhile, negative basic science experiments have generally used vastly supra-physiological concentrations of SSRIs, such that toxic effects on beta-cells are unsurprising. Thus, there have been reports that SSRIs such as fluoxetine impair β-cell metabolic coupling and/or insulin secretion in vitro (46, 47), but fluoxetine concentrations up to 100μM were used in these studies, considerably higher than the fluoxetine steady state concentration in plasma of 0.3-2.6μM (48). By contrast, basic science research using physiological concentrations of SSRIs has indicated that fluoxetine has direct peripheral effects stimulatory effects on

mouse and human islets in vitro to increase insulin secretion and improve β-cell mass (49).

**Interpretation**

Our findings suggest that short-term use of SSRIs is metabolically safe and may even improve glycaemic control. With 8 included studies, results for fluoxetine are the most rigorous. Out of the other SSRIs, only escitalopram/citalopram had a positive overall effect, although this is cautioned by a lower number of studies. Though likewise limited in power to detect a significant effect, the raw effect size (-0.19) for paroxetine was notably less promising, although the inclusion of some insulin-dependent patients in 2 of the 3 studies may have blunted this effect (10, 31). However, given that glycaemia was generally a secondary outcome of included studies, future trials are needed that are powered specifically for this measure and thereby confirm our findings. The relative paucity of data for non-fluoxetine SSRIs emphasises the need for trials of these agents for glycaemia. In particular, sertraline is commonly used for depression and positive effects on glycaemia have been reported by other clinical trials and some basic science research (50, 51).

Although benefits on glycaemia were not significant in patients without established diabetes in our analysis, such effects were limited by a lower number of studies for non-diabetes samples, which were also generally of shorter duration. Furthermore, their better glycaemia at baseline may have led to a floor effect in treatment response. Therefore, there is a need for 6-12-month trials of SSRIs targeted at patients at a high risk of diabetes.

Of the possible mechanisms by which SSRIs could improve glycaemia, weight loss – itself a consistent finding in our analysis – did not correlate with improvement in glycaemia across studies. An alternative explanation is that improved glycaemia resulted from increased insulin secretion following SSRI treatment. In this case, greater benefit may be achieved by targeting patients with established diabetes: unlike patients with pre-diabetes, whose insulin secretion is largely preserved, patients with established diabetes exhibit markedly reduced insulin secretion (52), whose improvement is the target of medications such as sulphonylureas. Our results suggest that SSRIs could have a similar role in augmenting insulin secretion in patients with non-insulin-dependent diabetes. This requires further research by future studies using repeated measures of insulin function in tandem with measures of glycaemia. Although findings did not vary significantly whether patients were selected for depression or not, there were fewer studies recruiting patients with depression in our synthesis. Therefore, it remains conceivable that some effects could occur through improvement in depression leading to improved self-care, treatment adherence and physical activity. Further studies targeting patients with depression are needed to test this model.

**Strengths and limitations**

Our review is strengthened by its systematic literature search, combined data collection on glycaemia measures and biological correlates, and the use of random-effects meta-analysis to account for heterogeneity. Including 16 studies enabled us for the first time to compare different SSRIs, to test effects on different populations and to conduct meta-regression analysis. Sensitivity analyses did not alter our findings. In selecting a far broader range of studies than previous meta-analyses, there is a risk that true treatment effects become harder to detect. However, our findings produced low overall

heterogeneity, which limited the ability of our meta-regression analyses to detect potential covariates of varying response, such as insulin resistance and weight loss. It should be stressed that the $I^2$ value is an estimate of heterogeneity that can be imprecise, particularly in smaller meta-analyses (53).Thus our calculated $I^2$ of 0% heterogeneity does not mean there is no heterogeneity between studies. The use of averages of patient characteristics instead of individual patient data for meta-regression may have resulted in ecological fallacy and further limited power to detect relationships (54). We accepted small trials in our inclusion criteria, although exclusion of these studies did not affect the overall result. Across studies, glycaemia was generally a secondary outcome, such that trials were not specifically powered to detect a significant change in glycaemia. Finally, the majority of studies were judged as having an unclear risk of bias in at least one domain, mostly due to lack of explicit intention-to-treat analysis and lack of detail on allocation concealment procedures.

**Conclusion**

Selective serotonin reuptake inhibitors, in particular fluoxetine and escitalopram/citalopram, have a positive overall effect on glycaemia, which is incompletely explained by effects on depression or weight loss across studies. Powered clinical trials of fluoxetine and other SSRIs of longer duration are now needed to confirm these findings, whilst also studying the underlying mechanisms.

## Author Contributions

All authors designed the research. TT, CDM and DS performed the statistical analyses. TT, CWPH and CDM performed the literature searches and risk of bias assessments. TT wrote the first draft. CDM, PMJ, SJP, KI, DS and CWPH revised the manuscript for important intellectual content. CDM had primary responsibility for the final content.


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## Declaration of interests

KI reports speaker fees from Eli Lilly, Janssen, Novo Nordisk and Sanofi.

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## FIGURE LEGENDS

**Figure 1**

PRISMA flow diagram summarising the literature search and study selection

**Figure 2**

Forest plot showing random effects meta-analysis of change in glycaemia for selective serotonin reuptake inhibitors versus placebo: stratified by medication type

**Figure 3**

Forest plot showing random effects meta-analysis of change in glycaemia for selective serotonin reuptake inhibitors versus placebo: stratified by diabetes status at baseline

**Figure 4**

Forest plot showing random effects meta-analysis of change in glycaemia for selective serotonin reuptake inhibitors versus placebo: stratified by depression status at baseline

**Figure 5**

Funnel plot to test publication bias. *'g'* represents Hedge's *g*; this was used for effect size estimates.

**Figure 1**

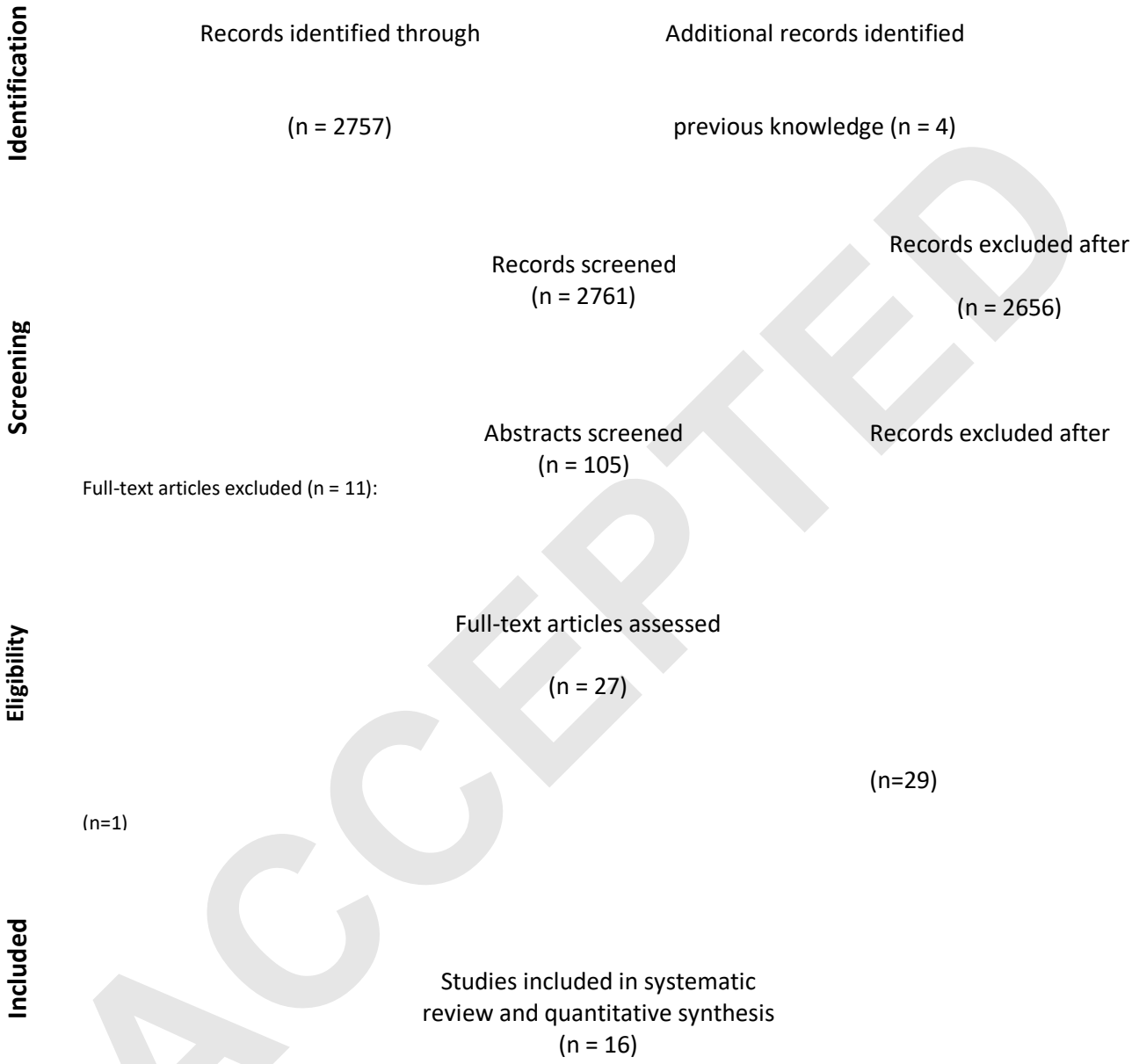

**Figure 2**

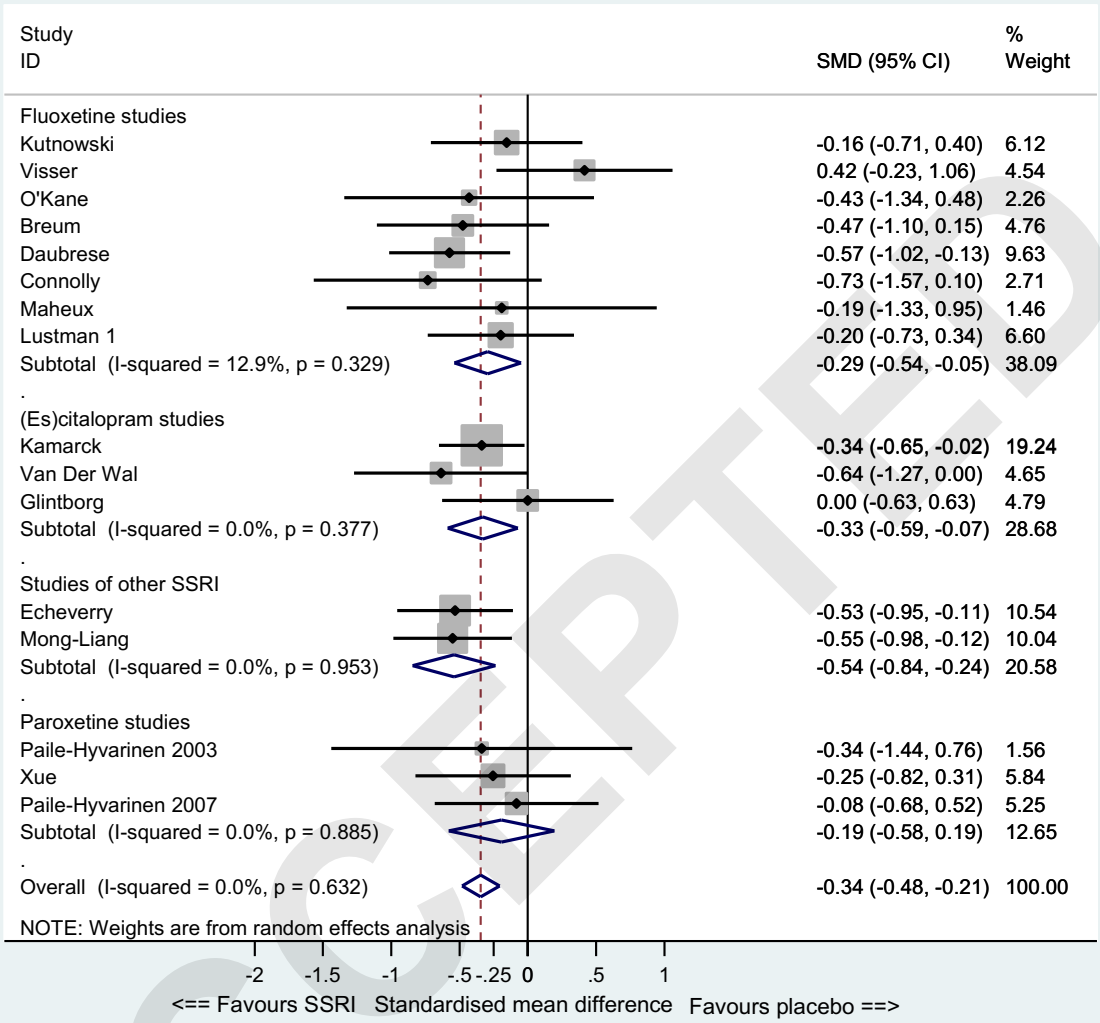

**Figure 3**

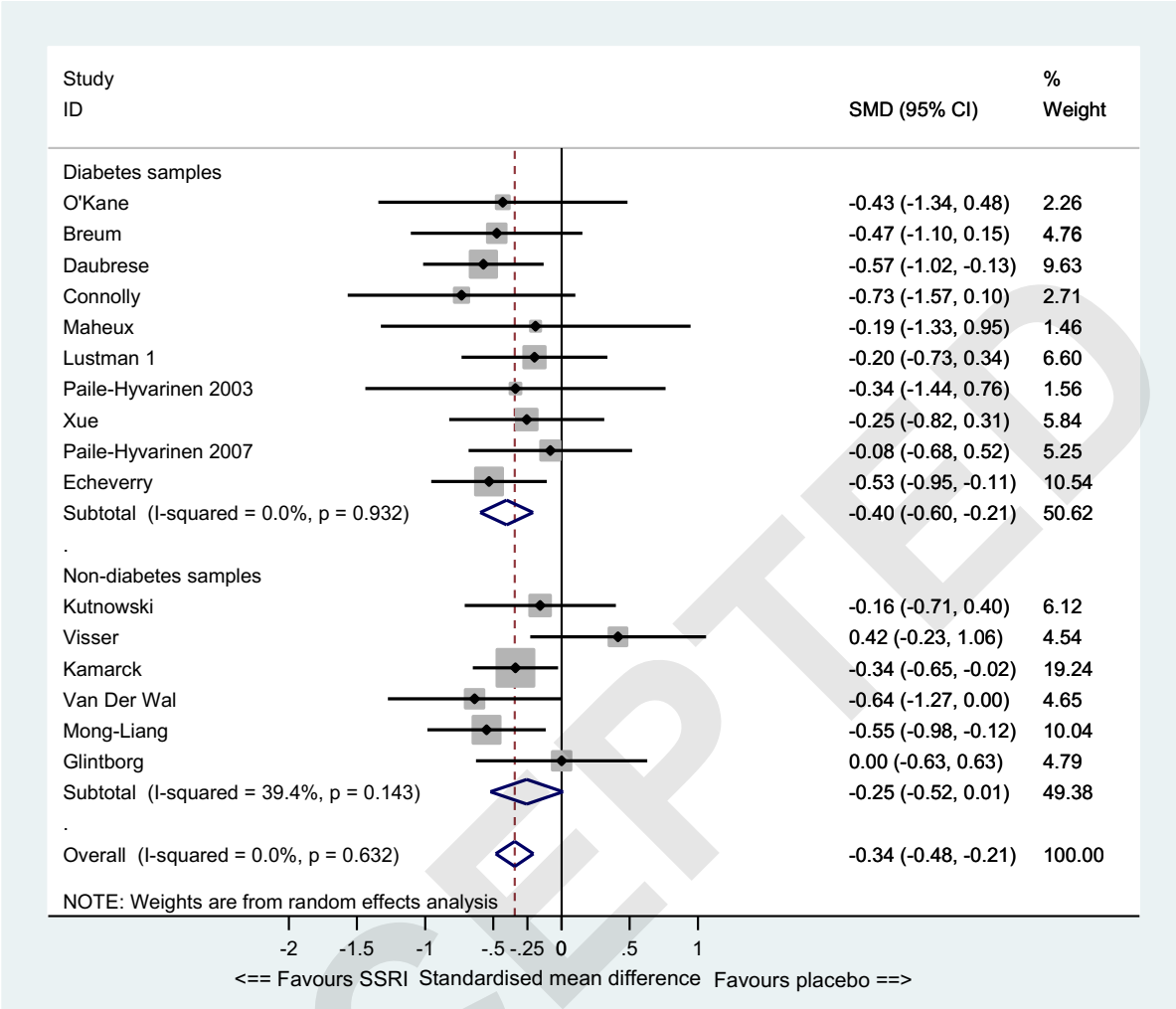

**Figure 4**

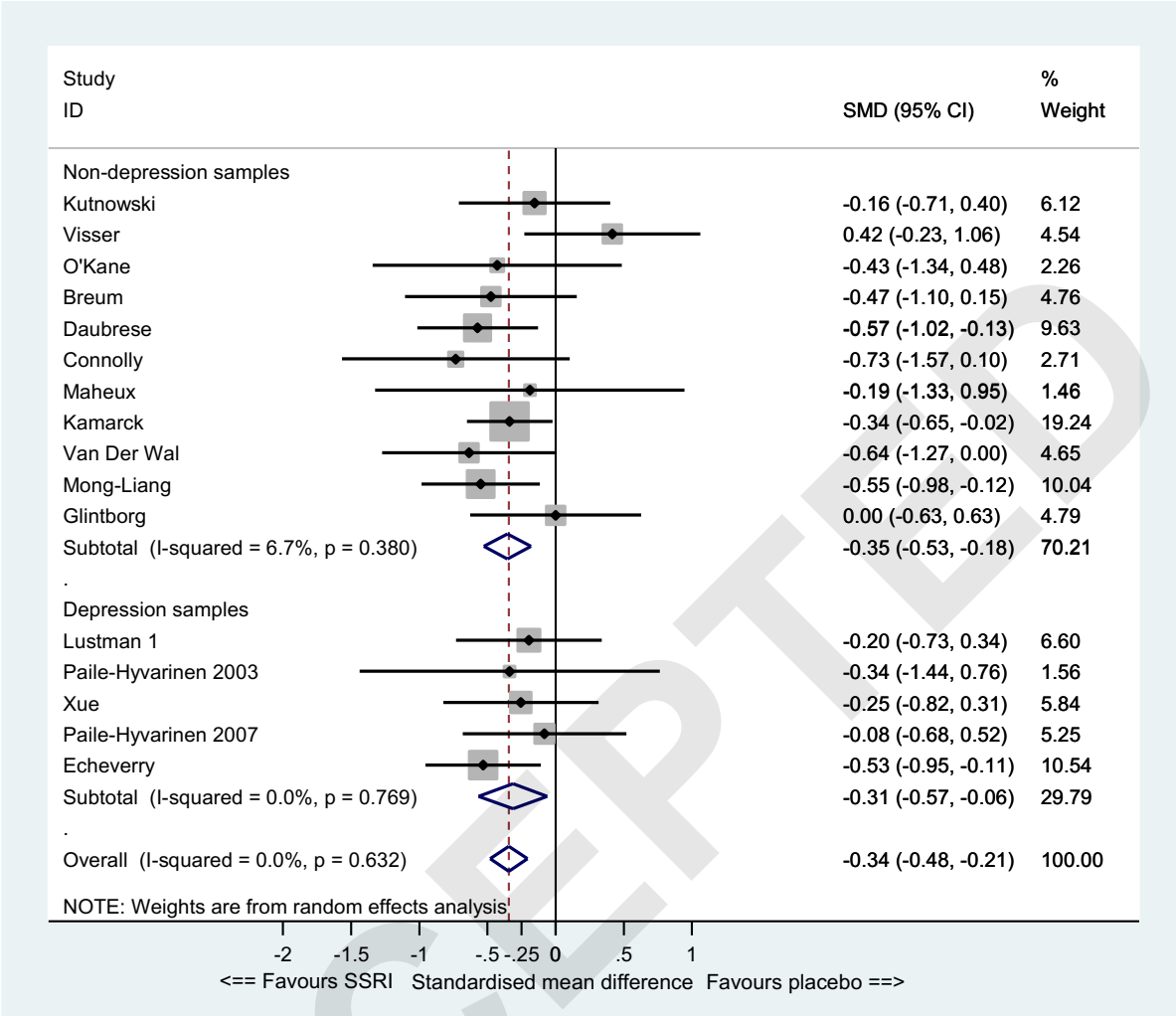

**Figure 5**

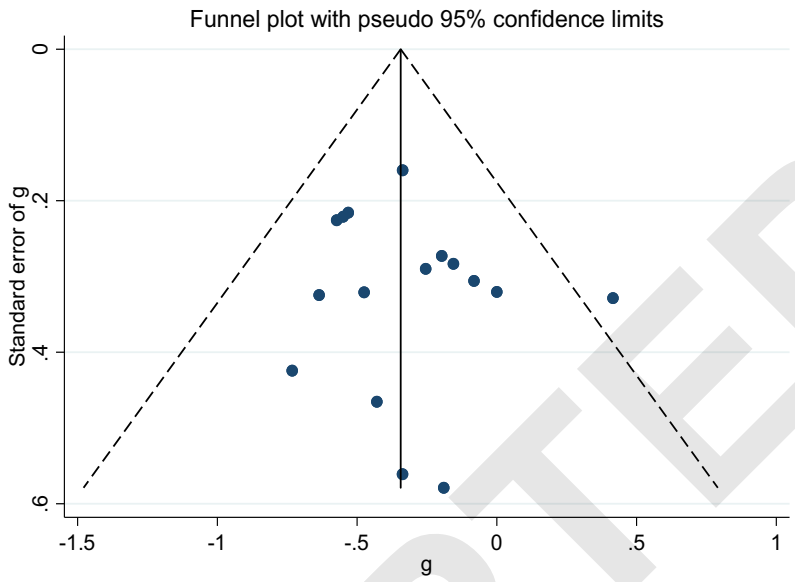

Table 1

*Summary characteristics of studies included in quantitative synthesis*

| Citation, Country of setting | Study design | Total sample size (male), mean age | Intervention (*n*), dose and duration | Control (*n*) and duration | Psychological inclusion criteria | Baseline diabetes status; other metabolic status | Mean baseline BMI ($kg/m^2$) | HOMA-IR baseline | HOMA-B baseline (%) | Was glycaemic control a primary or secondary outcome? |
|---|---|---|---|---|---|---|---|---|---|---|
| **Citalopram or escitalopram** | | | | | | | | | | |
| Kamarck et al. (2011), US | Double-blind, placebo- | 159 (79), N/R | Citalopram (*n* = 81), 40mg/d for 2 | Placebo (*n* = 78) for 2 months | High hostility (anger) scores on | No selection | 29.53 (5.64) | 3.64 (3.67) | 172.75 (N/R) | Primary outcome |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | controlled RCT | | months | | questionnaires | | | | | |
| Vander Wal, Gang, Griffing and Gadde (2012), US | Double-blind, placebo-controlled RCT | 40 (19), 45.00 (13.02) | Escitalopram (*n* = 20), 20mg/d for 12 weeks | Placebo (*n* = 20) for 12 weeks | Night Eating Syndrome (NES), ≥ 25 on NES-questionnaire | No selection | 32.95 (6.92) | N/R | N/R | Secondary outcome |
| Glintborg et al. (2018), Denmark | Double-blind, placebo-controlled RCT | 39 (0), 31.00 (6.00) | Escitalopram (*n* = 20), 20mg/d for 12 weeks | Placebo (*n* = 19) for 12 weeks | None | No selection; but selected for overweight premenopausal women with Polycystic Ovary | 35.80 (6.50) | 4.80 (2.40) | 229.00 (126.00) | Secondary outcome |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Syndrome | | | | |
| **Fluoxetine** | | | | | | | | | | |
| Breum, Bjerre, Bak, Jacobsen and Astrup (1995), Denmark | Double-blind, placebo-controlled RCT | 40 (12), 43.95 (9.27) | Fluoxetine (*n* = 20), 60mg/d for 12 months | Placebo (*n* = 20) for 12 months | None | T2DM or Impaired glucose tolerance (WHO criteria 1985); obesity | 38.20 (4.60) | 8.98 (N/R) | 103.64 (N/R) | Secondary outcome |
| Connolly et al. (1995), UK | Double-blind, placebo-controlle | 24 (15), 65.91 (N/R) | Fluoxetine (*n* = 11), 60mg/d for 6 months | Placebo (*n* = 13) for 6 months | None | Diet-controlled T2DM (HbA1c | 31.73 (N/R) | N/R | N/R | Secondary outcome |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | d RCT | | | | | <14%) | | | | |
| Daubresse et al. (1996), Belgium | Double-blind, placebo-controlled RCT | 82 (N/R), 52 (10.42) | Fluoxetine (*n* = 39), 60mg/d for 8 weeks | Placebo (*n* = 43) for 8 weeks | None | T2DM; obesity | 34.24 (4.85) | 9.72 (N/R) | 68.12 (N/R) | Secondary outcome |
| Kutnowski et al. (1992), Belgium[a] | Double-blind, placebo-controlled RCT | 50 (N/R), 50.52 (10.76) | Fluoxetine (*n* = 25), 60mg/d for 8 weeks | Placebo (*n* =25) for 8 weeks | None | Impaired glucose tolerance (Oral glucose tolerance test, 120 min blood glucose > 6.7mmol/L) | 34.35 (4.60) | N/R | N/R | Secondary outcome |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lustman, Freedland, Griffith and Clouse (2000), US | Double-blind, placebo-controlled RCT | 54 (16), 46.35 (12.25) | Fluoxetine (*n* = 27), 40 mg/d for 8 weeks | Placebo (*n* = 27) for 8 weeks | Major depressive disorder, ≥ 14 on BDI or HAM-D | T2DM and minority T1DM | N/R | N/R | N/R | Secondary outcome |
| Maheux, Ducros, Bourque, Garon and Chiasson (1997), Canada | Double-blind, placebo-controlled RCT | 12 (8), 54.5 (11.09) | Fluoxetine (*n* = 6), 60mg/d for 4 weeks | Placebo (*n* = 6) for 4 weeks | None | T2DM; obesity | 33.20 (6.52) | 15.65 (N/R) | 94.23 (N/R) | Secondary outcome |

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|---|---|---|---|---|---|---|---|---|---|---|
| O'Kane, Wiles and Wales (1994), UK | Double-blind, placebo-controlled RCT | 19 (6), 57.13 (N/R) | Fluoxetine (*n* = 9), 60mg/d for 12 months | Placebo (*n* = 10) for 12 months | None | T2DM; obesity | 36.27 (N/R) | N/R | N/R | Secondary outcome |
| Visser, Seidell, Koppeschaar and Smits (1993), Netherlands | Double-blind, placebo-controlled RCT | 38 (38), 40.6 (6.79) | Fluoxetine (*n* = 18), 60mg/d for 12 weeks | Placebo (*n* =20) for 12 weeks | None | No selection for diabetes; but selected for obesity and high abdominal fat distribution | 27.9 (1.17) | 2.17 (N/R) | 89.26 (N/R) | Secondary outcome |
| **Fluvoxamine** | | | | | | | | | | |
| Lu, Chen, | Double- | 85 (61), | 50mg/d | Placebo with | None; but | No selection | N/R | 2.14 | 84.98 | Secondar |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Kuo, Hsu and Chen (2017), Taiwan | blind, placebo-controlled RCT | 44.88 (8.98) | Fluvoxamine with 100mg/d clozapine (*n* = 43) for 12 weeks (combination therapy) | 300 mg/d clozapine (*n* = 42) for 12 weeks (monotherapy) | selected for schizophrenia (DSM-IV) | | | (1.98) | (N/R) | y outcome |
| **Paroxetine** | | | | | | | | | | |
| Paile-Hyvärinen, Wahlbeck and Eriksson | Single-blind, placebo-controlled RCT | 13 (0), 61.65 (10.04) | Paroxetine (*n* = 7), 20mg/d for 10 weeks | Placebo (*n* = 6) for 10 weeks | Mild depression (MADRS 2.5-12) | T2DM (HbA1c < 6.5%) | 30.91 (4.81) | N/R | N/R | Primary outcome |

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|---|---|---|---|---|---|---|---|---|---|---|
| (2003), Finland | | | | | | | | | | |
| Paile-Hyvärinen, Wahlbeck and Eriksson (2007), Finland | Double-blind, placebo-controlled RCT | 43 (33), 59.34 (5.69) | Paroxetine (*n* = 20), 20mg/d for 6 months | Placebo (*n* = 23) for 6 months | Mild depression (no more than 6 symptoms, DSM-IV) | T2DM (HbA1c > 7.0%) | 31.84 (5.41) | N/R | N/R | Primary outcome |
| Xue (2004), China[b] | Double-blind, placebo-controlled RCT | 48 (20), Could not be acquired | Paroxetine (*n* = 24), 40mg/d for 8 weeks | Placebo (*n* = 24) for 8 weeks | Major depressive disorder | T2DM and minority T1DM | N/R | N/R | N/R | Secondary outcome |

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| **Sertraline** | | | | | | | | | | |
| Echeverry, Duran, Bonds, Lee and Davidson (2009), US | Double-blind, placebo-controlled RCT | 89 (24), 52.5 (9.00) | Sertraline (*n* = 45), 50mg/d to 100mg/d for 6 months | Placebo (*n* = 44) for 6 months | Major depressive disorder | T2DM and minority T1DM | N/R | N/R | N/R | Primary outcome |

*Notes*: Data is presented as mean, with the standard deviation in parenthesis, unless indicated otherwise. Abbreviations: BDI, Beck's Depression Inventory; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder (4th edition); HAM-D, Hamilton Rating Scale for Depression; MADRS, Montogomery-Asberg's Depression Rating Scale; N/R, not reported; N/S, not significant. a) Glucose-intolerant subset of study analysed only, due to potential overlap between the diabetes subset in the study by Daubresse et al. (1996). b) The study by Xue (2004) was published in Chinese; as translation could not be acquired, data extraction was limited.

Table 2

*Risk of Bias in included studies, evaluated by the Cochrane Collaboration tool*

| First author, Year, Country, | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and researchers (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting bias (reporting bias) | Other bias | Summary assessment of risk of bias for the whole study |
|---|---|---|---|---|---|---|---|---|
| **Citalopram or escitalopram** | | | | | | | | |
| Kamarck, 2011, US | **Low risk** Randomised | **Low risk** Central | **Low risk** Blinding of | **Low risk** Blinding of | **Low risk** ITT analysis; | **Low risk** All | **Unclear risk** Participation | **Low risk** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | allocation using a omputer generated randomisation list | pharmacy-controlled allocation, with concealment of allocation in a confidential envelope | participants and key study personnel | outcome assessment ensured, and unlikely that blinding could have been broken | all drop-outs were reported and reasons were stated | predetermined outcomes were reported | bias due to a potential difference between volunteers and those who did not return the postcard | |
| Vander Wal, 2012, US | **Low risk** Randomised allocation using | **Low risk** Central pharmacy-controlled | **Low risk** Blinding of participants and key | **Low risk** Blinding of outcome assessment | **Low risk** ITT analysis; no patients dropped out | **Low risk** All predetermined outcomes | **Unclear risk** Participants were recruited from those responding | **Low risk** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | computer-generated block randomisation | allocation | study personnel | ensured, and unlikely that blinding could have been broken | from the study | were reported | to advertisements-participation bias | |
| Glintborg, 2018, Denmark | **Unclear risk** Randomisation reported but method not described | **Low risk** Central pharmacy-controlled allocation | **Low risk** Blinding of participants and key study personnel | **Low risk** Blinding of outcome assessment ensured, and unlikely that blinding could have been broken | **High risk** Although reasons for drop-outs were defined, ITT was not conducted | **Low risk** All predetermined outcomes were reported | **Unclear risk** Funded by Lundbeck and Novo Nordisk pharmaceutical companies | **Unclear risk** Involvement of pharmaceutical companies and lack of ITT analysis may influence results |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Fluoxetine** | | | | | | | | |
| Breum, 1995, Denmark | **Unclear risk** Randomisation reported but method not described | **Unclear risk** Unknown | **Low risk** Blinding of participants and key study personnel | **Low risk** Blinding of outcome assessment ensured, and unlikely that blinding could have been broken | **Unclear risk** Unknown if ITT analysis was performed, but did report drop-outs and reasons | **Low risk** All predetermined outcomes were reported | **Unclear risk** Funded by Eli Lilly and Co (pharmaceutical company) | **Unclear risk** Involvement of pharmaceutical companies and lack of ITT analysis may influence results |
| Connolly, 1995, UK | **Unclear risk** Randomisation reported but | **Unclear risk** Unknown | **Low risk** Double-blind | **Low risk** Double-blind | **High risk** Although the reasons for | **Low risk** All predetermine | **Unclear risk** Funded by Lilly industries | **Unclear risk** Involvement of |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | method not described | | | drop-outs were defined, they were excluded from analysis | d outcomes were reported | (pharmaceutical company) | pharmaceutical companies and lack of ITT analysis may influence results |
| Daubresse, 1996, Belgium | **Unclear risk** Randomisation reported but method not described | **Unclear risk** Unknown | **Low risk** Blinding of participants and key study personnel | **Low risk** Blinding of outcome assessment ensured, and unlikely that blinding could have | **High risk** Asymmetry in the reasons for drop-outs and intention to treat-analysis not performed. | **Low risk** All predetermined outcomes were reported | **Unclear risk** Unclear how the participants were recruited | **Unclear risk** |

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|---|---|---|---|---|---|---|---|---|
| | | | | been broken | | | | |
| Kutnowski, 1992, Belgium | **Low risk** ‘Randomisation was balanced by blocks of 4’ | **Unclear risk** Unknown | **Low risk** Double-blind | **Low risk** Double-blind | **Low risk** ITT analysis; all drop-outs and reasons were stated | **Low risk** All predetermined outcomes were reported | **Unclear risk** Eli Lilly Benelux provided the drugs and monitored with assistance | **Unclear risk** Involvement of pharmaceutical company may positively influence the results with fluoxetine |
| Lustman, 2000, USA | **Low risk** Randomised allocation using computer | **Unclear risk** Unknown | **Low risk** Blinding of participants and key | **Low risk** Blinding of outcome assessment | **Low risk** Although ITT analyses was not | **Low risk** All predetermined outcomes | **Unclear risk** Eli Lilly Indiana funded this study | **Low risk** Involvement of pharmaceutica |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | generated randomisation | | study personnel | ensured, and unlikely that blinding could have been broken | implemented, no significant differences between completers and non completers of study; all drop-outs and reasons were defined | were reported | | l company may positively influence the results with fluoxetine |
| Maheux, 1997, Canada | **Unclear risk** Randomisation occurred but method not | **Unclear risk** Unknown | **Low risk** Blinding of participants and key | **Low risk** Blinding of outcome assessment | **Unclear risk** Unclear whether ITT analysis was | **Low risk** All predetermined outcomes | **Unclear risk** Eli Lilly Canada funded this study | **Unclear risk** Involvement of pharmaceutica |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | described | | study personnel | ensured, and unlikely that blinding could have been broken | implemented, or whether there were any drop-outs/exclusions from analysis | were reported | | l companies, lack of ITT analysis and lack of defining drop-outs may influence results |
| O'Kane, 1994, UK | **Unclear risk** Randomisation occurred but method not described | **Unclear risk** Unknown | **Low risk** Double-blind | **Low risk** Double-blind | **High risk** Three participants dropped out, however ITT analysis was | **Low risk** All predetermined outcomes were reported | **Unclear risk** Lilly industries funded this study. | **Unclear risk** Involvement of pharmaceutical companies and lack of |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | not implemented. Reasons for drop-outs were specified. | | | ITT analysis may influence results |
| Visser, 1993, Netherlands | **Unclear risk** Randomisation occurred but method not described | **Unclear risk** Unknown | **Low risk** Double-blind | **Low risk** Double-blind | **High risk** Two participants dropped out, reasons were stated but ITT analysis was not implemented | **Unclear risk** Did not report adverse effects, although this was a pre-specified outcome | **Unclear risk** One of the authors was from Eli Lilly Netherlands. | **Unclear risk** Involvement of pharmaceutical companies and lack of ITT analysis may influence results |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Fluvoxamine** | | | | | | | | |
| Lu, 2017, Taiwan | **Low risk** Randomised allocation using computer generated stratified block randomisation | **Low risk** Central computer-generated allocation of treatment, with treatment delivered in coded containers. | **Low risk** Blinding of participants and key study personnel | **Low risk** Blinding of outcome assessment ensured, and unlikely that blinding could have been broken | **Low risk** ITT analysis; all drop-outs and reasons were stated | **Low risk** All predetermined outcomes were reported | **Low risk** | **Low risk** |
| **Paroxetine** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Paile-Hyvärinen, 2003, Finland | **Low risk** Randomised allocation using computer generated randomisation | **Unclear risk** Allocation reported to have been concealead, but the method of concealment was not adequately described | **Low risk** Blinding of participants and clinicians, but not investigators. | **High risk** Investigators were not blinded- so may have introduced detection bias | **High risk** No ITT analysis, as 2 drop-outs not included in analysis; although reasons were defined | **Low risk** All predetermined outcomes were reported | **Unclear risk** Did not state exactly how the researchers recruited participants; possible participation bias | **Unclear risk** |
| Paile-Hyvärinen, 2007, | **Low risk** Randomised allocation | **Low risk** Central pharmacy- | **Low risk** Blinding of participants | **Low risk** Blinding of outcome | **High risk** ITT analysis not | **Low risk** All predetermine | **Unclear risk** GlaxoSmithKline funded the | **Unclear risk** Involvement of |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Finland | using computer generated randomisation | controlled allocation | and key study personnel | assessment ensured, and unlikely that blinding could have been broken | implemented as only those who completed study were analysed; although reasons for drop-out were defined | d outcomes were reported | study and provided the drugs; competing interest | pharmaceutical companies and lack of ITT analysis may influence results |
| **Sertraline** | | | | | | | | |
| Echeverry, 2009, USA | **Low risk** Randomised allocation | **Unclear risk** Allocation | **Low risk** Blinding of participants | **Low risk** Blinding of outcome | **Low risk** ITT analysis and reasons | **Low risk** All predetermine | **Low risk** | **Low risk** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | using computer generated randomisation | reported to have been concealead, but the method of concealmen t was not adequately described | and key study personnel | assessment ensured, and unlikely that blinding could have been broken | for drop-outs were defined | d outcomes were reported |

*Notes*: The risk of bias for each domain, with reasons, has been presented in this table. If the summary risk of bias was unclear, a justification was given. Abbreviations: ITT, Intention To Treat.

Table 3

*Changes in glycaemia, weight, and adverse effects, following treatment with Selective Serotonin Reuptake Inhibitors compared to control groups*

| Study author, year and country | Intervention vs. control group | Change in glycaemia for intervention group (SD) | Change in glycaemia for placebo group (SD) | *P*-value for comparing change in glycaemia between intervention and placebo groups | Measure of glycaemic control | Change in weight in SSRI group (kg) | Adverse effects[a] |
|---|---|---|---|---|---|---|---|
| **Citalopram or escitalopram** | | | | | | | |
| Kamarck, 2011, US | Citalopram vs Placebo | -0.13 (N/R) mmol/L | +0.08 (N/R) mmol/L | $p = 0.020$ | FBG | -0.26 | N/S |
| Vander Wal, 2012, US | Escitalopram vs Placebo | +0.22 (0.35) mmol/L | +0.42 (0.26) mmol/L | $p = 0.577$ | FBG | -0.43 | N/S |

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|---|---|---|---|---|---|---|---|
| Glintborg, 2018, Denmark | Escitalopram vs Placebo | 0.00 (0.70) mmol/L | 0.00 (0.60) mmol/L | $p$ = N/S | FBG | N/R | N/S |
| **Fluoxetine studies** | | | | | | | |
| Breum, 1995, Denmark | Fluoxetine vs Placebo | -2.10 (3.60) mmol/L | -0.80 (1.20) mmol/L | $p$ = N/R | FBG | -10.1 | N/S |
| Connolly, 1995, UK | Fluoxetine vs Placebo | -0.80 (3.48) mmol/L | +1.20 (1.63) mmol/L | $p$ = N/S | FBG | -3.9 | N/S |
| Daubresse, 1996, Belgium | Fluoxetine vs Placebo | -1.70 (2.83) mmol/L | -0.02 (2.97) mmol/L | $p < 0.001$ | FBG | -3.1 | Significantly more patients experienced tremor in |

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|---|---|---|---|---|---|---|---|
| | | | | | | | fluoxetine group |
| Kutnowski, 1992, Belgium[b] | Fluoxetine vs Placebo | -0.12 (0.55) mmol/L | -0.03 (0.59) mmol/L | *p* = N/S | FBG | N/R | N/R for subgroup analysed |
| Lustman, 2000, USA | Fluoxetine vs Placebo | -0.40 (1.65) % | - 0.07 (1.65) % | *p* = 0.130 | HbA1c | +6.09 | N/S |
| Maheux, 1997, Canada | Fluoxetine vs Placebo | -1.10 (2.79) mmol/L | -0.40 (3.92) mmol/L | *p* = N/S | FBG | -0.5 | N/S |
| O'Kane, 1994, UK | Fluoxetine vs Placebo | -0.30 (1.78) mmol/L | -0.50 (1.78) mmol/L | *p* = N/S | FBG | N/R | N/S |
| Visser, 1993, | Fluoxetine vs | -0.02 (0.19) | -0.12 (0.27) | *p* = N/S | FBG | -5.9 | N/R |

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|---|---|---|---|---|---|---|---|
| Netherlands | Placebo | mmol/L | mmol/L | | | | |
| **Fluvoxamine studies** | | | | | | | |
| Lu, 2017, Taiwan | Fluvoxamine and clozapine vs Placebo and clozapine | -0.02 (0.73) mmol/L | +0.50 (1.11) mmol/L | $p < 0.001$ | FBG | +0.7 | N/S |
| **Paroxetine studies** | | | | | | | |
| Paile-Hyvärinen, 2003, Finland | Paroxetine vs Placebo | -1.47 (2.52) mmol/L | -0.78 (0.58) mmol/L | $p = 0.720$ | FBG | -0.71 | N/R |
| Paile-Hyvärinen, 2007, Finland | Paroxetine vs Placebo | -0.20 (3.56) mmol/L | +0.10 (3.65) mmol/L | $p$ = N/R | FBG | -0.5 | N/R |

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|---|---|---|---|---|---|---|---|
| Xue, 2004, China | Paroxetine vs Placebo | -0.50 (1.49) % | -0.10 (1.60) % | *p* = N/S | HbA1c | N/R | N/R |
| **Sertraline studies** | | | | | | | |
| Echeverry, 2009, USA | Sertraline vs Placebo | -2.00 (2.10) % | -0.90 (2.00) % | *p* = 0.003 | HbA1c | -0.045 | N/R |

*Notes*: Data are presented as mean, with the standard deviation in parenthesis, unless indicated otherwise. Abbreviations: FBG; Fasting blood glucose; HbA1c, glycosylated haemoglobin; N/R, not reported; N/S, not significant; SD, standard deviation; vs., versus. a) Adverse effects only reported when there was a significantly greater incidence in the intervention group compared to control group. b) Glucose-intolerant subset of study analysed only due to potential overlap between the diabetes subset in the study by Daubresse et al. (1996).